General

Guideline Title

Genetic counseling and testing for *FMR1* gene mutations: practice guidelines of the National Society of Genetic Counselors.

Bibliographic Source(s)

Finucane B, Abrams L, Cronister A, Archibald AD, Bennett RL, McConkie-Rosell A. Genetic counseling and testing for FMR1 gene mutations: practice guidelines of the National Society of Genetic Counselors. J Genet Couns. 2012 Dec;21(6):752-60. [50 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Genetic counselors play a pivotal role in providing pre-test information to individuals at significantly increased risk for Fragile X Mental Retardation-1 (*FMR1*) gene mutations (see table below); preparing them for possible outcomes; reporting results and educating them about *FMR1*-associated disorders; and facilitating communication among family members. Counseling families with *FMR1* mutations requires a solid understanding of X-linked inheritance in the context of trinucleotide repeat instability and a changing clinical landscape. In addition to the known challenges of addressing informational and psychosocial aspects of a genetic condition, counseling for *FMR1* mutations poses additional specific issues in a number of areas.

Table: Pre-Test Genetic Counseling for *FMR1* Mutations

General	• Assess awareness and knowledge about Fragile X Mental Retardation-1 (*FMR1*)-related disorders • Regardless of family history or clinical presentation, discuss possibility and implications of detecting alleles in the premutation, full mutation, and intermediate ranges • Review anticipated follow-up options in case a mutation or intermediate allele is found • Discuss anticipated emotional reactions to test results, including implications specific to the patient's current stage of life
Known family history of	• Elicit patient's experience with *FMR1* mutations in family, including attitudes toward disability

FMR1 mutations	• Assess self-perception of genetic risk • Use family history to illustrate inheritance patterns • Where appropriate, include at-risk minor children in the counseling discussion • Assist parents to carefully weigh medical and emotional benefits of *FMR1* testing against potential harms in pre-symptomatic children and teens
Adults with cognitive/behavioral Impairment	• Identify Fragile X syndrome (FXS) or Fragile X-associated tremor/ataxia syndrome (FXTAS)-related neurological symptoms that may impact patient's understanding and decision-making • Ascertain guardianship status of adult prior to testing when appropriate • Include family member or caretaker in the discussion with the patient's permission • Access legal and social work resources for questions involving competency and informed consent for genetic testing
Prenatal testing	• Alert patient that follow-up amniocentesis may be needed to further clarify chorionic villus sampling (CVS) results

Counseling Considerations

- Centers offering population screening should ensure that they have the resources available to provide pre- and post-test genetic counseling that supports the psychosocial and clinical needs of the patient and family. In light of widespread *FMR1* testing among women without known risk factors, genetic counselors should anticipate seeing patients who did not receive any pre-test information, have no prior knowledge of *FMR1*-associated disorders, and are unprepared to learn that they have an *FMR1* mutation.
- Although many genetic counselors are familiar with Fragile X syndrome (FXS), fewer have experience with Fragile X-associated tremor/ataxia syndrome (FXTAS) and Fragile X-associated primary ovarian insufficiency (FXPOI). As such, they may underestimate the scope of clinical inquiry needed for risk assessment in families with *FMR1* mutations. Taking a pedigree in these families requires attention to a diverse constellation of developmental, neurodegenerative, and reproductive symptoms that vary widely in age of onset and severity across multiple generations. Specific family history queries designed to identify individuals with the full spectrum of *FMR1* gene mutations are listed in Table 7 in the original guideline document. Given the subjective nature of behavioral and cognitive symptoms, psychiatric and educational records should be obtained whenever possible to confirm a reported history of developmental issues.
- The diagnosis of *FMR1*-associated disorders can have far-reaching genetic and emotional implications for extended family members. When an *FMR1* mutation is identified in a family, genetic counselors should assist patients in developing strategies to inform relatives.
- Parents should be encouraged to explore open and meaningful discussion with their children about *FMR1*-associated disorders and genetic risk. Genetic counselors should work toward helping parents develop a positive, resilient communication style which may aid in the long-term adaptation of children to *FMR1*-related risk.
- Psychiatric issues, as well as cognitive decline, are common among patients with FXTAS. They may experience confusion and emotional reactions to learning the genetic nature of their condition and its implications for their children and other relatives. With the patient's consent, it may be important to involve other family members and caregivers in these discussions so that genetic and management information is accurately communicated.
- Patients who have normal laboratory results should be counseled that *FMR1* testing does not rule out other genetic conditions or determine the cause of undiagnosed developmental disabilities, infertility, or neurodegenerative disorders in other family members.

Intermediate Alleles

- Conflicting research on the phenotypic and reproductive complications of intermediate alleles makes it difficult for genetic counselors to provide clear cut guidance to these patients. Counseling in these situations should include a discussion of known reproductive and clinical implications of intermediate alleles. In the absence of further data to the contrary, the focus should be on the low rate of instability and limited evidence to indicate increased risk for developing *FMR1*-associated disorders.
- Patients with intermediate alleles who present with clinical signs suggestive of *FMR1*-associated disorders should be counseled about the likely possibility of an unrelated etiology for their symptoms and referred, as indicated, for additional diagnostic work-up.
- Intermediate alleles are common and often detected coincidentally as part of an infertility work-up, through general population screening in women without a family history of *FMR1* mutation disorders, or in children undergoing evaluation of developmental delay or autism. Genetic counselors should anticipate a heightened level of anxiety and reactions in these patients, particularly since many have had little or no pre-test counseling to prepare them for the result.

Reproductive Issues

- Prenatal diagnosis should be offered to women with pre- or full mutations. Males with premutation alleles should receive genetic counseling about potential phenotypic risks to their daughters, all of whom will inherit premutations.
- Genetic counselors should be alert to female family members who could be pursuing fertility treatments while unaware that they have an underlying *FMR1* premutation and a risk for having children with FXS.
- Since a main determinant of successful pre-implantation genetic diagnosis (PGD) is ovarian function, women with *FMR1* premutations should be evaluated for subfertility prior to consideration of PGD.
- At this time, there are no reports of intermediate alleles expanding to full mutations in a single generation, and invasive prenatal diagnosis is not medically indicated. Despite this, some patients with intermediate alleles, especially if they are already pursuing prenatal diagnosis for another indication, request fragile X prenatal testing to confirm that the fetus does not have a full mutation. Less frequently, patients may ask for prenatal testing to determine if an intermediate allele is unstable and has expanded into a premutation, based on concerns about potential phenotypic features, most of which would manifest in adulthood, if at all. In these circumstances, genetic counseling is crucial given the issues surrounding prenatal testing for adult onset disorders and the inability to predict the premutation phenotype.

Treatment and Resources

- In light of the rapid pace of drug development for FXS, genetic counselors need to be informed about current research on targeted pharmaceuticals. While these are still in the research phase, genetic counselors can facilitate the informational process and help families consider both positive and negative aspects of enrolling in a clinical research study.
- The National Fragile X Foundation (www.fragileX.org) provides extensive educational resources and support for families and professionals. The Foundation maintains a Facebook social networking site for families affected by Fragile X-associated disorders, as well as a separate informational site for individuals with FXTAS (www.fxtas.org).
- FRAXA Research Foundation (www.fraxa.org) raises funds to accelerate research progress toward effective treatments, and it also supports families and raises awareness about FXS.
- The Fragile X Clinical and Research Consortium (www.fxcrc.org) fosters the international development of Fragile X specialty clinics and provides a structure for collaborative research efforts, including drug trials. Families should be encouraged to contact the consortium to locate their nearest FXCRC center about clinical management of FXS and other *FMR1*-related disorders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

- Fragile X syndrome (FXS)
- Other Fragile X Mental Retardation-1 (*FMR1*)-associated disorders, including Fragile X-associated tremor/ataxia syndrome (FXTAS), Fragile X-associated primary ovarian insufficiency (FXPOI), and other premutation-associated issues

Guideline Category

Counseling

Diagnosis

Risk Assessment

Screening

Clinical Specialty

Family Practice

Internal Medicine

Medical Genetics

Obstetrics and Gynecology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Social Workers

Guideline Objective(s)

To assist genetic counselors in providing accurate risk assessment and appropriate educational and supportive counseling for individuals with positive test results and families affected by Fragile X Mental Retardation-1 (*FMR1*)-associated disorders

Target Population

- Individuals undergoing Fragile X Mental Retardation-1 (*FMR1*) testing, including those with known or unknown risk factors for *FMR1* gene mutation
- Individuals with positive test results for *FMR1* gene mutation and families affected by *FMR1*-associated disorders

Interventions and Practices Considered

1. Providing pre- and post-test genetic counseling that supports the psychosocial and clinical needs of the patient and family
2. Counseling on the known reproductive and clinical implications of intermediate alleles
3. Counseling on reproductive issues
    - Offering prenatal diagnosis to women with pre- or full mutations
    - Counseling males about potential phenotypic risks to their daughters
    - Alerting female family members who could be pursuing fertility treatments while unaware that they have an underlying Fragile X Mental Retardation-1 (*FMR1*) premutation
    - Evaluating women with *FMR1* premutations for subfertility before consideration of pre-implantation genetic diagnosis (PGD)
4. Providing educational and supportive resources to families concerning Fragile X syndrome (FXS) and associated disorders

Major Outcomes Considered

- Prevalence of Fragile X Mental Retardation-1 (*FMR1*) gene mutations
- Accuracy of diagnostic and screening tests
- Effectiveness of genetic counseling approach and information (including intermediate allele risks, reproductive issues, supportive organizations and new treatment options)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The guideline authors searched PubMed from 2005 to 2010. Since this is an update to the previously published Fragile X Mental Retardation-1 (*FMR1*) practice guideline by the same author group (plus or minus a few authors), the group included some of the key references from the original publication. Even after the literature review, the authors discussed and incorporated new literature as it was published. As experts in the field of *FMR1* mutations and fragile X, the author group was generally aware of new significant publications on this topic.

Articles covering laboratory and clinical aspects of *FMR1* mutations were used. Articles included a mix of landmark papers, original research, and reviews in the publication.

Specific terms included (but were not limited to): fragile X, *FMR1* mutations, FXTAS, premutation, full mutation, intermediate allele, autism, intellectual disability, FXPOI, infertility, newborn screening, prenatal diagnosis, X-linked, trinucleotide repeats, genetic counseling, neurodevelopmental disorders, and targeted pharmaceuticals.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Not stated

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The guideline developers reviewed a published cost analysis.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

Evidence to support the recommendations was compiled from research studies as well as established standards for Fragile X Mental Retardation-1 (*FMR1*) testing.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Improved genetic counseling and testing for individuals and families affected by Fragile X Mental Retardation-1 (*FMR1*)-associated disorders

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

The practice guidelines of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist genetic counselors and other health care providers in making decisions about appropriate management of genetic concerns, including access to and/or delivery of services. Each practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable. As such, information and recommendations within the NSGC practice guidelines reflect the current scientific and clinical knowledge at the time of publication, are only current as of their publication date, and are subject to change without notice as advances emerge. In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome. Genetic counseling practice guidelines are never intended to displace a health care provider’s best medical judgment based on the clinical circumstances of a particular patient or patient population. Practice guidelines are published by NSGC for educational and informational purposes only, and NSGC does not "approve" or "endorse" any specific methods, practices, or sources of information.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Dec

Guideline Developer(s)

National Society of Genetic Counselors - Medical Specialty Society

Source(s) of Funding

National Society of Genetic Counselors

Guideline Committee

National Society of Genetic Counselors Practice Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available to subscribers from the Journal of Genetic Counseling Web site .

Availability of Companion Documents

The following is available:

- Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns 2008 Oct;17(5):424-33. Available to subscribers from the Journal of Genetic Counseling Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on November 1, 2013. The information was verified by the guideline developer on November 11, 2013.

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